Accuracy assessment of the CNAO dose delivery system in the initial period of clinical activity and impact of later improvements on delivered dose distributions

Title: Accuracy assessment of the CNAO Dose Delivery System in the initial period of clinical activity and impact of later improvements on delivered dose distributions

Short running title: CNAO DDS accuracy assessment

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Abstract

Purpose: The retrospective analysis of the Dose Delivery System (DDS) performances of the initial clinical operation at CNAO (Centro Nazionale di Adroterapia Oncologica) is reported, and compared with the dose delivery accuracy following the implementation of a position feedback control.

Methods: Log files and raw data of the DDS were analyzed for every field of patients treated with protons and carbon ions between 01/2012 and 04/2013 (~3800 fields). To investigate the DDS accuracy, the spot positions and the number of particles per spot measured by the DDS and prescribed by the Treatment Planning System were compared for each field.

The impact of deviations on dose distributions was studied by comparing, through the gamma-index method, two 3D physical dose maps (one for prescribed, one for measured data), generated by a validated dose computation software. The maximum gamma and the percentage of points with

gamma ≤ 1 (passing volume) were studied as a function of the treatment day, and correlated with the deviations from the prescription in the measured number of particles and spot positions. Finally, delivered dose distributions of same treatment plans were compared before and after the implementation of a feedback algorithm for the correction of small position deviations, to study the effect on the delivery quality.

The double comparison of prescribed and measured 3D maps, before and after feedback implementation, is reported and studied for a representative treatment delivered in 2012, re-delivered on a PMMA block in 2018.

Results. Systematic deviations of spot positions, mainly due to beam lateral offsets, were always found within 1.5 mm, with the exception of the initial clinical period**.** The number of particles was very stable, as possible deviations are exclusively related to the quantization error in the conversion from monitor counts to particles. For the chosen representative patient treatment, the gamma-index evaluation of prescribed and measured dose maps, before and after feedback implementation, showed a higher variability of maximum gamma for the 2012 irradiation, with respect to the re-irradiation of 2018. However, the 2012 passing volume is > 99.8% for the sum of all fields, which is comparable to the value of 2018, with the exception of one day with 98.2% passing volume, probably related to an instability of the accelerating system.

Conclusions. A detailed retrospective analysis of the DDS performances in the initial period of CNAO clinical activity is reported. The spot position deviations are referable to beam lateral offset fluctuations, while almost no deviation was found in the number of particles. The impact of deviations on dose distributions showed that the position feedback implementation and the increased beam control capability acquired after the first years of clinical experience lead to an evident improvement in the DDS stability, evaluated in terms of gamma-index as measure of the impact on dose distributions. However, the clinical effect of the maximum gamma variability found in the 2012 representative irradiation is mitigated by averaging along the number of fractions, and the high

percentage of passing volumes confirmed the accuracy of the delivery even before the feedback implementation.

Keywords: charged particle therapy, pencil beam scanning, dose delivery accuracy

Introduction

The first Italian hospital-based charged particle therapy facility (Centro Nazionale di Adroterapia Oncologica, CNAO, Pavia) started clinical activity with protons in September 2011 and one year later with carbon ions, and treated more than 2500 patients at the time of this writing.

The full 3D dose delivery is provided by a dedicated synchrotron with modulated scanning ion beam technique (*pencil beam scanning)*, consisting of superposition of thousands of pencil beams of different directions and energies.

During the treatment planning process, the target volume is segmented into iso-energetic layers at different water equivalent depths in tissue. At the time of dose delivery, the layers are scanned by a sequence of pristine beams, named *spots* in the following, of discrete energy, necessary to deposit the required dose at the desired depth, delivering for each spot a defined number of particles at a specific position[1].

To guarantee the irradiation of each spot with the prescribed properties, a dose delivery system (DDS) is needed to monitor and control the beam position and the number of delivered particles for each spot, to control the steering magnets used to scan the treated volume laterally, and to control the sequence of spills provided by the accelerator[2].

The results of the first year of treatment at CNAO have been already reported from the clinical point of view[3] and from the one of patient-specific quality assurance (QA) checks[4], while a detailed study of the accuracy and performance of the DDS has never been reported so far and it is therefore the object of the present work.

It is well-known that the highly conformal dose distribution achieved with active scanned pencil beams has its counterpart in intrinsic sensitivity to delivery uncertainties, and that the accurate delivery of the treatment as prescribed by the treatment planning system (TPS) is crucial to achieve the desired clinical outcomes[5].

The main effort in reducing uncertainties is routinely focused on patient-related sources of errors, i.e. repositioning, related setup imaging, immobilization techniques, identifying anatomical changes and consequently adapting plans[6]. Moreover, daily checks and corrections, if needed, are performed to control potential systematic effects in pencil beam position, size and energy, as well as on the number of delivered particles[7].

Omitting the aforementioned uncertainties due to patient positioning, anatomical changes, and residual systematic effects, particle beam scanning systems deliver the dose with a degree of accuracy depending on the accuracy of position, energy and intensity of the beam extracted from the accelerator and delivered to the target. In addition, finite scan speeds, beam intensity non-uniformities, beam monitoring constraints, and magnet operations all contribute to the inaccuracy of the delivery[8].

The effect of variable machine performance on delivery quality and on the other inaccuracies of the delivery system can be studied through the careful analysis of treatment log files[9,10]. These files contain the record of the machine parameters for a given field delivery of a given fraction, consisting in the measured positions and measured charge of the monitor chambers, expressed in terms of monitor counts, for each spot[10,11]. Previous studies have demonstrated that treatment log files created by spot scanning beam delivery systems can be used to determine the inaccuracies of the delivered fraction[10,11], providing a thorough understanding of the performance of the system and its stability in time[2].

The aim of this work is twofold: it first reports the dose delivery accuracy of the first 15 months of clinical operation at CNAO and secondly it compares it with the dose delivery accuracy achieved after the system upgrade. This comparison is performed in terms of the impact on the dose

distributions, to evaluate the improvement resulting from the implementation of a beam position feedback algorithm inside the DDS. This work exploited the rare opportunity of having full access to TPS data, treatment plans and DDS data (raw data of monitor chambers and treatment log files).

The first goal has been achieved by using the treatment log files to compare prescribed number of particles per spot and spot positions with corresponding measured quantities, for every field of patients treated between January 2012 and April 2013 (more than 3800 fields) with protons and carbon ions. To evaluate the impact on dose distributions of deviations between prescribed and measured quantities, TPS reference values and corresponding values measured by monitor chambers were used as input of a validated dose calculation tool[12]. The correspondence between the 3D dose maps has been quantified by means of the gamma-index criterion[13], and the results have been reported for one representative patient treated with protons. Finally, to study the effect on delivery quality of the implementation of a feedback algorithm for the correction of small position deviations, delivered dose distributions of the same treatment plans before and after feedback implementation have been compared. To this aim, the same representative treatment was repeated on a PMMA block used to dump the beam, and the dose comparison was performed with the acquired data.

Materials and Methods

Brief overview of the CNAO Beam Line

The CNAO synchrotron accelerates ions to a range of kinetic energies (60–250 MeV for protons, 120–400 MeV/u for carbon ions) corresponding to depths in water from 30 to 320 mm for protons and from 30 to 270 mm for carbon ions, with steps of 2 mm for both[14].

Three treatment rooms are available at CNAO, two with horizontal fixed beam line (room 1 and room 3) and the third one with both horizontal and vertical fixed lines (room 2), resulting in 4 independent beam lines and dose delivery systems[14].

After the extraction at selected energy from the synchrotron, the particles are sent to the appropriate beam line to reach the desired treatment room. The last two magnetic elements along the line are two identical dipole magnets, located approximately 5.5 m upstream the isocenter, to scan horizontally and vertically each layer of the target volume with the pencil beam scanning approach.

The commercial Syngo RT Planning TPS (Siemens AG Healthcare, Erlangen, Germany), is used for plan optimization and calculation, and the DDS guides the irradiation according to the sequence of spots defined by the TPS.

The DDS in use at CNAO has been designed, built, and commissioned by CNAO, Istituto Nazionale di Fisica Nucleare (INFN) and University of Torino. Its main components are two independent beam monitoring detectors, called BOX1 and BOX2, placed downstream the vacuum exit window of the beam line, interfaced with two control systems performing real-time fast and slow control, and connected, among others, to the scanning magnets and to a beam chopper. BOX1 consists of a large-area parallel plate ionization chamber (240x240 mm^2 sensitive area) to measure the number of beam particles and two strip chambers (128 strips with a pitch of 1.65 mm) to measure the beam position, while BOX2 consists of the same large-area parallel plate chamber of BOX1 and a pixel chamber (32x32 pixels with a pitch of 6.6 mm) used for redundancy.

A comprehensive description of the components, essential tasks and operations performed by the DDS has been reported by Giordanengo et al[2].

Treatment Planning System to Dose Delivery data conversion

The TPS groups spots with the same energy into a single slice and generates a plan with all the fields to irradiate, specified in terms of particles per spot and 2D spot positions (x-y, in mm) for the different iso-energy layers in the target volume. At each treatment session, patient treatment data are sent to the dose delivery controller as a text file, through the Mosaiq (Elekta, Sunnyvale, USA) Oncology Information System (OIS) and a custom interface. Before the treatment delivery, plan data are

converted by the DDS into number of monitor counts, position in strips units on the plane of the strip chambers and the scanning magnet currents are calculated as a function of requested energy (in power supply current units).

During the delivery, the data from the monitor chambers acquired by the DDS are used to check the beam position, the number of delivered particles and to control the magnets and the accelerator at the end of each spot and slice, respectively. At the end of each treatment delivery, these raw data are used to create the required treatment record and stored to be used later for the off-line analysis. These data contain for each spot the measured average beam position and the corresponding monitor counts. A reversed conversion into the format of the TPS parameters is applied to the DDS measurements to provide the treatment log file in the proper units for direct comparison with the prescriptions within the OIS.

The data conversion procedure between DDS and TPS data is described in detail in Giordanengo et al.[2] and is shortly summarized in the following.

Number of particles vs number of monitor counts. The amount of charge released in the gas by particles interaction is measured in real-time by large-area parallel plate ionization chambers[15] and saved in monitor counts spot by spot, where each count refers to a minimum collected charge of 200 fC. This charge quantum corresponds, as an example in a particular nozzle of CNAO and at reference conditions for temperature and pressure, to a number of protons ranging from 7.2×10^3 at the energy of 62 MeV to 1.9×10^4 at the energy of 226 MeV; similarly, the range of the number of carbon ions extends from 341 at the energy of 115 MeV/u to 767 at 399 MeV/u. This correspondence is determined during DDS commissioning and checked during dosimetric and calibration procedures, as described in detail in Mirandola et al[7]. Corrections for temperature and pressure are applied when the plan is converted.

Beam position at the isocentric plane vs strip chambers' reference system. To convert the positions at the isocentric plane reference system (in mm) to the chambers' one (in strip units), the divergence

of the beam, i.e. the beam angle after the scanning magnets, and measurements of the rotation and translation of the monitor chambers planes with respect to the isocentric plane were experimentally determined during DDS commissioning. Since the relation between the two reference systems could be affected by a tilt of the extracted beam, the correct position of the non-deflected pencil beam (nominal zero position) with respect to the isocenter is verified during daily QA, as reported in Mirandola et al[7].

Beam position at the isocentric plane vs currents for the scanning magnet power supplies. For each of the two particle species, the beam position at the isocentric plane was measured during DDS commissioning, by varying the magnet current and the beam energy. The required parameters for the conversion were found through a fitting procedure. During daily QA the spot position is tested across the whole scanning area, according to the procedure described in Mirandola et al.[7], and the test is passed if the deviation from the nominal position is within ±1 mm. At the beginning of the clinical operations at CNAO, before the onset of the automatic position correction based on the feedback of the monitoring system, the correction of possible position offsets observed in the QA procedures was achieved by adding a constant position offset to this initial data conversion.

Position feedback correction

The beam position is reconstructed from the measurements of the BOX1 strip chambers using a center of gravity algorithm, when a minimum number of 100 counts is reached. This corresponds to 10^5-10^6 protons, and to an average time of 4 ms (range 1-8 ms, according to the instantaneous beam intensity). The difference between the so obtained beam position and the prescribed one is continuously monitored by the DDS during the spot irradiation. Whenever such a difference exceeds a pre-defined threshold (2 mm), an interlock signal is issued, which immediately pauses the irradiation. As reported in Giordanengo et al.[2], the position interlock has to be manually reset by the operator for restarting the treatment. However, if the interlock persists the treatment has to be aborted. In summer 2013, i.e. few months after the patient treatments considered in this work, an online feedback correction of the

beam position was introduced to compensate for slow drifts of the beam position, presumably due to the non-perfect dispersion at the isocenter and to small variations of the momentum along the spill. Such small drifts sometimes lead to longer treatment times due to the occurrence of one or more beam interlocks during the treatment. The method used is to convert the position difference into a current offset value sent to the scanning system, which applies the correction. The applied correction at one position is maintained as starting correction value for the next positions of the same beam energy and same spill, where it can be updated. The current offset is reset when a new spill is generated. Whenever the correction exceeds the threshold of 3 mm, an interlock signal is issued, which pauses the irradiation. The spot position is measured twice: the first time to check the need of correction, and eventually generate an interlock, the second time to calculate the position of the complete spot to be reported in the log file. If the number of counts is below the minimum threshold required to reconstruct the beam position with the center of gravity method, no feedback is applied and the spot position of the strip with the largest number of counts is returned in the log file.

The described position correction approach is a self-correcting system, where the same detector used for the position measurement (strip chambers) is also used for the correction. Such detector is not placed at the isocenter. Therefore, the effectiveness of the correction method at the isocenter could be evaluated through the QA checks of the spot position at the isocenter and across the scan field. These QA checks are daily performed by the medical physics staff to verify the consistency between the reference system (i.e. the isocenter) and the one of the strip chambers, using the all-in-one PTW phantom loaded with strips of an EBT3 film for spot [7].

As already mentioned, to verify the correct position of the non-deflected pencil beam (nominal zero position) with respect to the isocenter, a specific test is performed during daily QA. Moreover, the accuracy of the pencil beam deflection by the scanning magnets across the whole scanning area is independently checked through a spot pattern with nine beam spots in nominal positions (8 peripheral and 1 central)[7].

For 84% of the daily QA sessions in the period January 2012-July 2013, before the feedback implementation, the spot positions were within tolerance (± 1 mm) both in the center and at the edges of the scan field, for all particles, energies, and beam lines. For all the daily sessions considered, the mean absolute deviations (± rms) for the central position were 0.6 ± 0.4 mm in X and 0.4 ± 0.3 mm in Y, and 0.6 ± 1.0 mm in X and 0.4 ± 0.3 in Y for the edge positions. Ignoring the daily sessions which didn't pass the test and required the steering of the extraction lines before the patient treatment, the mean absolute deviations (± rms) for the central position were 0.5 ± 0.3 mm in X and 0.3 ± 0.2 mm in Y, and 0.4 ± 0.3 mm in X and 0.3 ± 0.2 in Y for the edge positions. The same analysis performed in the period July 2017-November 2018, after feedback implementation, showed an increase in the percentage (94%) of the daily QA sessions with spot positions within tolerance (± 1 mm) both in the center and at the edge positions. For all the daily sessions considered, the mean absolute deviations (± rms) for the central position were 0.5 ± 0.3 mm in X and 0.5 ± 0.4 mm in Y, and 0.5 ± 0.3 mm in X and 0.5 ± 0.4 in Y for the edge positions. The same analysis, ignoring the daily sessions which didn't pass the QA test, results in a mean absolute deviation (± rms) of 0.4 ± 0.3 mm in X and 0.4 ± 0.3 mm in Y for the central position, and 0.4 ± 0.3 mm in X and 0.5 ± 0.3 in Y for the edge positions.

Correction of delivered particle numbers in the log files

The treatment log file, provided by the DDS at the end of each treatment, is based on the DDS raw data stored during the field delivery.

The analysis performed for this work used log files and raw data of the DDS produced during the initial clinical activity. More specifically, the raw data saved by the DDS at the end of each spill are used to correct for the two following systematic effects, inherent in the data saved in the log files. It should be observed that later versions of the DDS are implementing such corrections when the log files are produced.

1) The system is designed so that whenever one of the two large-area parallel plate ionization chambers reaches the prescribed number of counts specified by the TPS, the delivery of the spot is terminated and the sequence is moved to the following spot. For the second chamber, used for redundancy and as a safety monitor, the prescribed number of counts is increased by 10% to let the first chamber alone trigger the end of the spot. It may be observed that, although very rarely and only at little requested counts, the second chamber can reach the prescription before the first chamber because of negative dark current effects in the first chamber, leading to a wrong count of particles. The information on which of the two large-area parallel plate chambers reached the prescribed dose is recorded in DDS raw data on a spot-by-spot basis, but the log file uses the data of the first chamber, so a correction was applied to account for this effect in the calculation of the number of particles delivered.
2) Because of noise and background current, mainly due to the leakage currents of the large-area parallel plate chambers, some counts are measured even without the beam, during the inter-spill time. These counts, either positive or negative, affect the dose delivered to the first spot of each spill, as they are added to the actual number of counts for that spot. Since the information about the dark counts measured in the inter-spill time is available in the raw data, it has been used to correct under- or over-counting of first spots on the log files.

Analysis of the treatment fields

3837 fields from all the 62 patients consecutively treated with protons and carbon ions between January 2012 and April 2013 have been analyzed. The range of values for the main delivery parameters is listed in Table 1.

265 ***Table 1. Analyzed Fields Statistics. Pat. = patient***

	N. patients	Total n. of fields	Fields/pat. (min-max)	Slices/pat. (min-max)	Spots/slice (min-max)	Prescribed particles/pat. (min-max)	Energy (min-max) [MeV/u]
proton	46	3411	15 - 147	848–9419	1–1145	4.85E+11–1.37E+13	62–227
carbon	16	426	4 - 60	120–2733	1–4628	1.27E+09 –2.06E+11	115–399

266

267 As a first step of this analysis, the accuracy of the DDS has been investigated by comparing for each
268 field both the positions of spots at the isocentric plane, determined from the strip chambers as
269 previously described, and the number of particles per spot measured by the DDS with the
270 corresponding prescriptions from the TPS. The analysis has been performed separately for treatments
271 delivered in room 1 and 3 and for protons and carbon ions in order to isolate possible systematic
272 effects due to the particle type or to the beam line and DDS. Room 2 has been commissioned in late
273 September 2013 and therefore wasn't considered in this study.

274 Secondly, these quantities have been used to create two 3D physical dose maps, one for the
275 prescription and one for measured data, by using a validated dose computation software[12]. The
276 correspondence of the two dose distributions has been evaluated with the gamma-index method using
277 a 2 mm grid spacing with 0.2 mm resolution, 2 mm Distance-To-Agreement (DTA) and 2% Dose
278 difference[13].

279 The analysis of the maximum gamma value and of the percentage of points with gamma ≤ 1 (*passing*
280 *volume*, in the following) was performed as a function of the day of the treatment. More specifically,
281 the analysis was performed separately for the two sets of daily fractions, which characterize the course

of the treatments analyzed: the first series of fractions (called *1st Phase*) and the second set (called *Boost)* delivered in the last days of treatment.

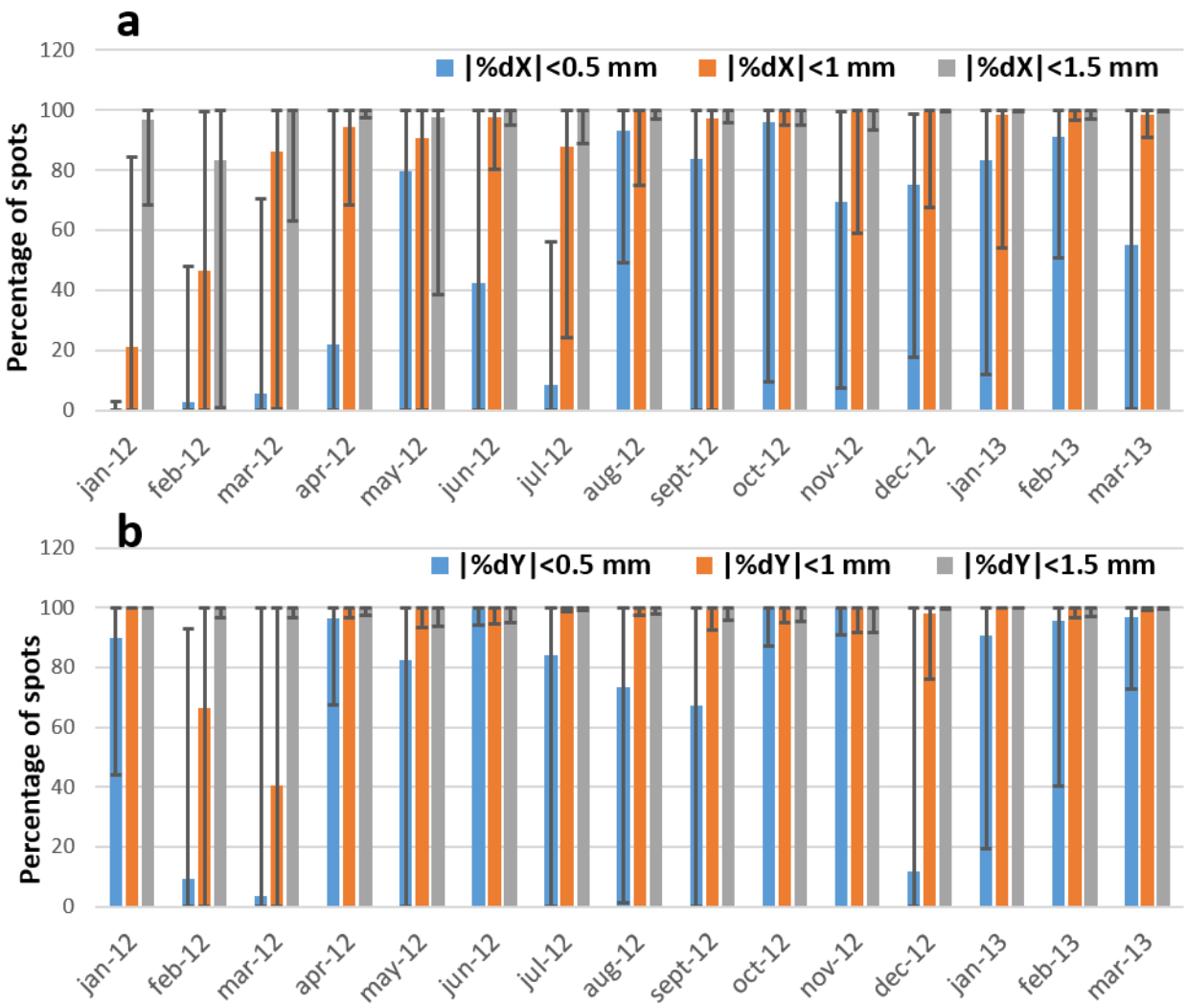
In both cases, the maximum gamma value and the *passing volume* for each individual field and for the sum of the different fields delivered in the same day were reported. In parallel, the correlation between the deviations observed in the measured number of particles or spot positions and the accuracy of delivered dose has been looked at.

As an example, the 3D maps comparison of prescribed and delivered dose is reported for a patient affected by chordoma of the skull base treated in room 1 (protons) with a total of 37 fractions. This patient was selected because representative of a treatment with deviations between prescribed and delivered dose distributions. The aim is twofold: to verify the effect of the spot position accuracy on the dose distribution and to study the impact of the online feedback correction of spot position deviations described earlier. For the latter study, the same treatment was repeated on a PMMA block, and the dose comparison was performed with the acquired data.

Results

Spot position accuracy

The absolute difference between the measured and prescribed spot positions at the isocentric plane have been studied separately in the horizontal (X) and vertical (Y) directions. The fraction of spots with such a difference within three different thresholds (0.5, 1, and 1.5 mm) has been calculated for each field irradiated between January 2012 and April 2013 in room 1 (protons) and 3 (protons and carbon ions). The results have been grouped per month of delivery and reported in Fig. 1, 2 and 3.



302

303 ***Figure 1. Mean value of the percentage of spots whose position differs from the prescription less than 0.5***

304 ***mm (blue bars), 1 mm (orange bars), 1.5 mm (gray bars), for all fields treated with protons in room1, along***

X direction (a) and Y direction (b). The minimum and maximum percentage values of the fields irradiated in each considered month are displayed as solid vertical bars for the three different thresholds.

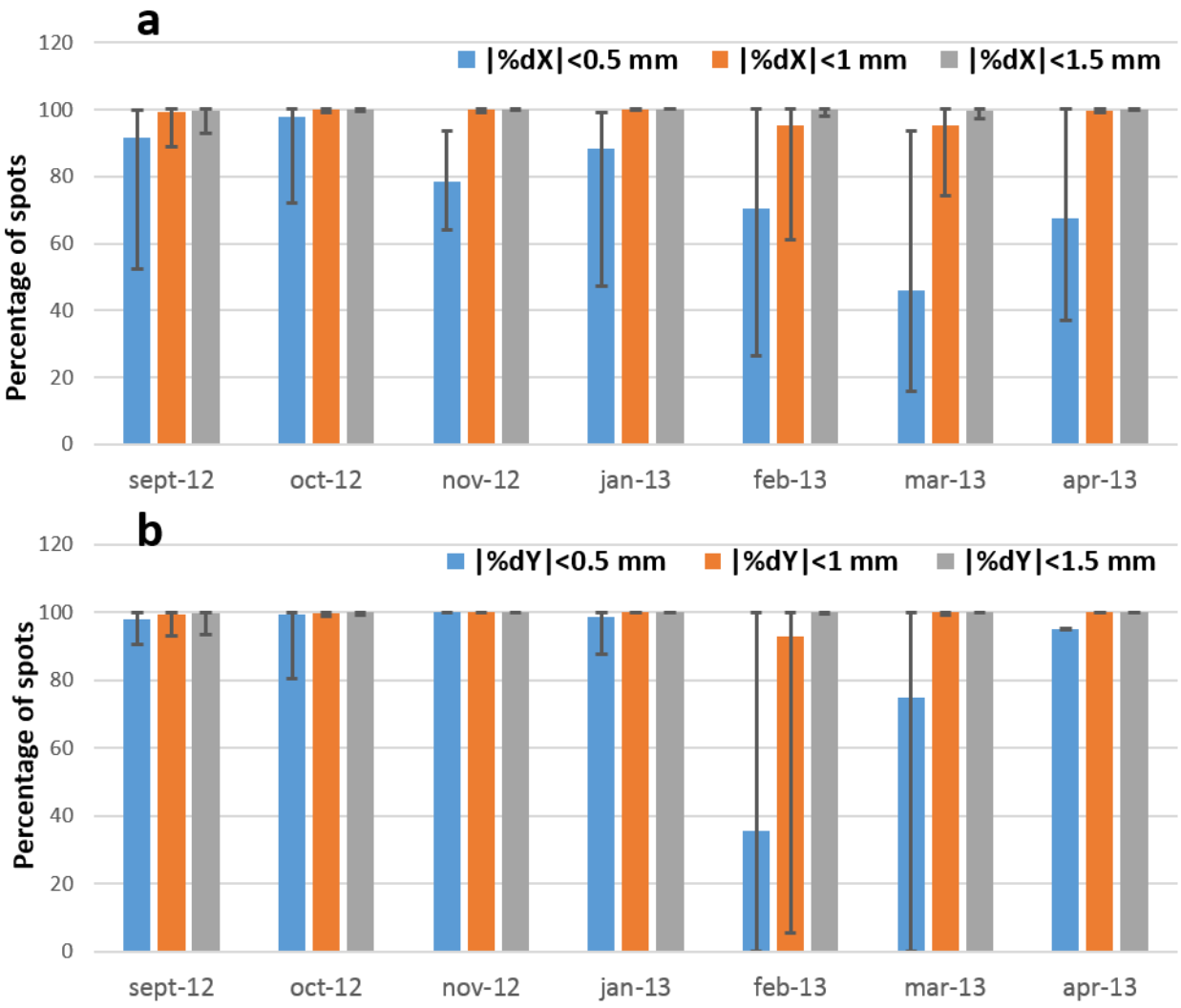


Figure 2: Mean value of the fraction of spots whose position differs from the prescription less than 0.5 mm (blue bars), 1 mm (orange bars), 1.5 mm (gray bars), for all fields treated with protons in room3, along X direction (a) and Y direction (b). The minimum and maximum percentage values of the fields irradiated in each considered month are displayed as solid vertical bars for the three different thresholds.

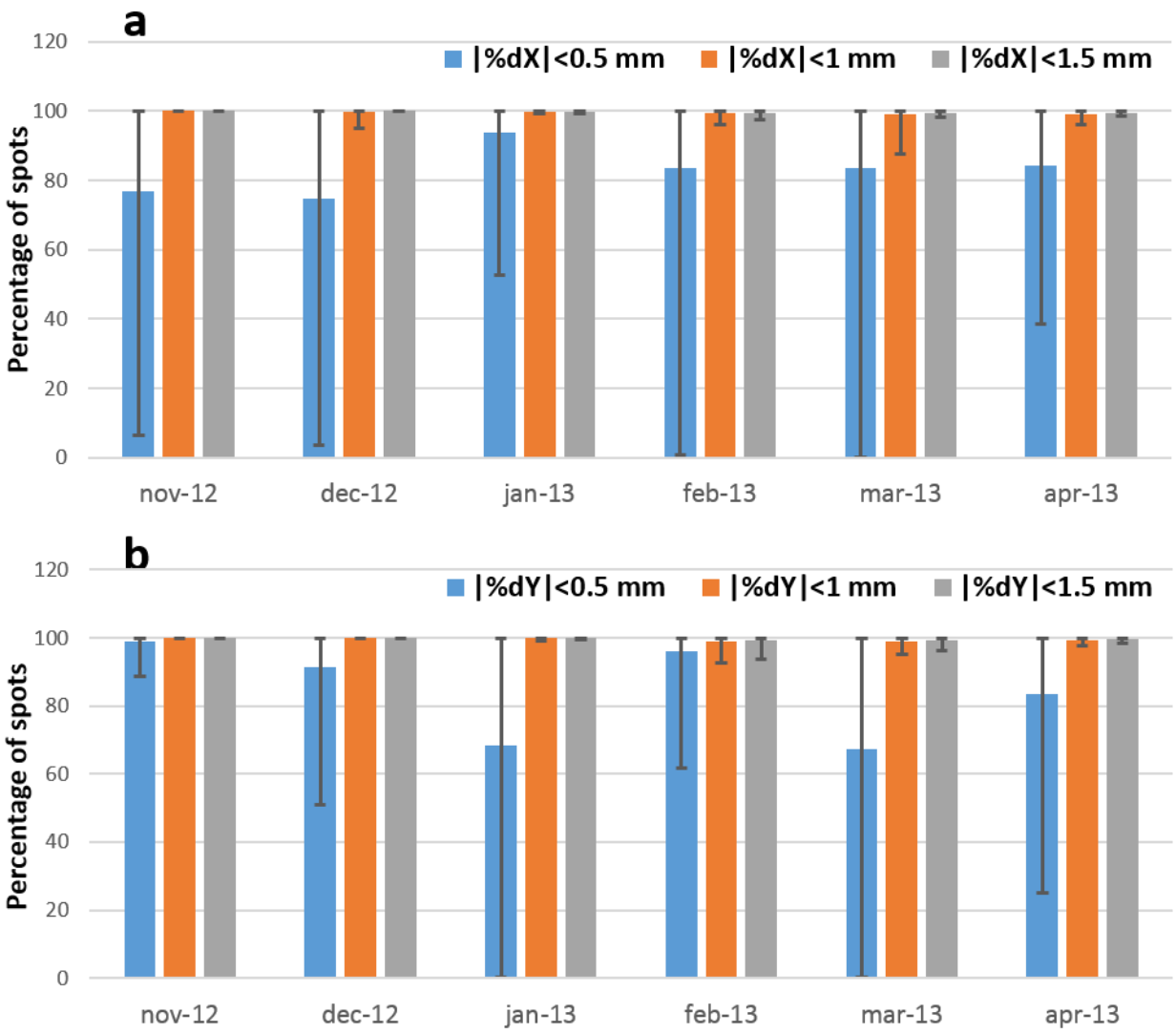


Figure 3: Mean value of the fraction of spots whose position differs from the prescription less than 0.5 mm (blue bars), 1 mm (orange bars), 1.5 mm (gray bars), for all fields treated with carbon ions in room3, along X direction (a) and Y direction (b). The minimum and maximum percentage values of the fields irradiated in each considered month are displayed as solid vertical bars for the three different thresholds.

Fig. 1, 2 and 3 show a better spot positioning stability in Y compared to X direction. This can be explained by the more complex beam dynamics in the horizontal plane, where the acceleration and the beam extraction occurs. It can also be noticed that few small tunings of the accelerator optics were necessary to realign the beam vertically in room 1. Indeed, as explained in Mirandola et al.[7], beam steering adjustments were performed when the beam optics was causing the results of daily checks to deviate more than twice the tolerance level or to remain out of tolerance for two consecutive days.

Accuracy of the number of particles delivered

The relative difference between the number of prescribed and delivered particles per spot was studied, and the percentage of spots with relative difference within three thresholds has been calculated for each irradiated field and is reported as function of treatment month in Fig. 4 for proton treatments in room 1, in Fig. 5a for proton treatments in room3 and in Fig. 5b for carbon ion treatments in room 3.

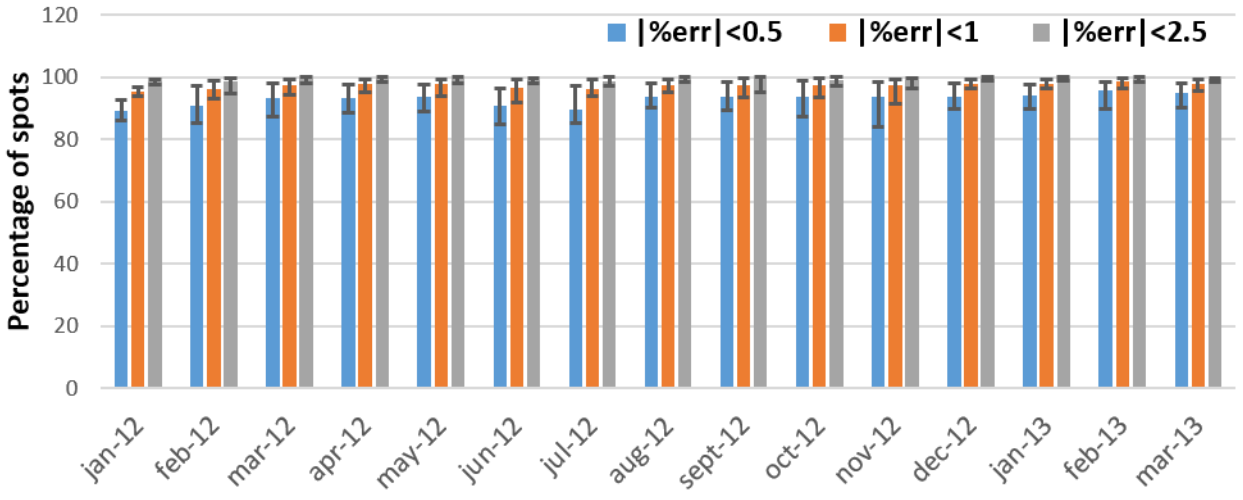


Figure 4: Mean value of the percentage of spots with relative difference between prescribed and delivered number of particles within three different tolerances: 0.5% (blue bars), 1% (orange bars), and 2.5% (gray bars) for all fields treated with protons in room 1. The minimum and maximum percentage values of the fields irradiated in each considered month are displayed as solid vertical bars for the three different thresholds.

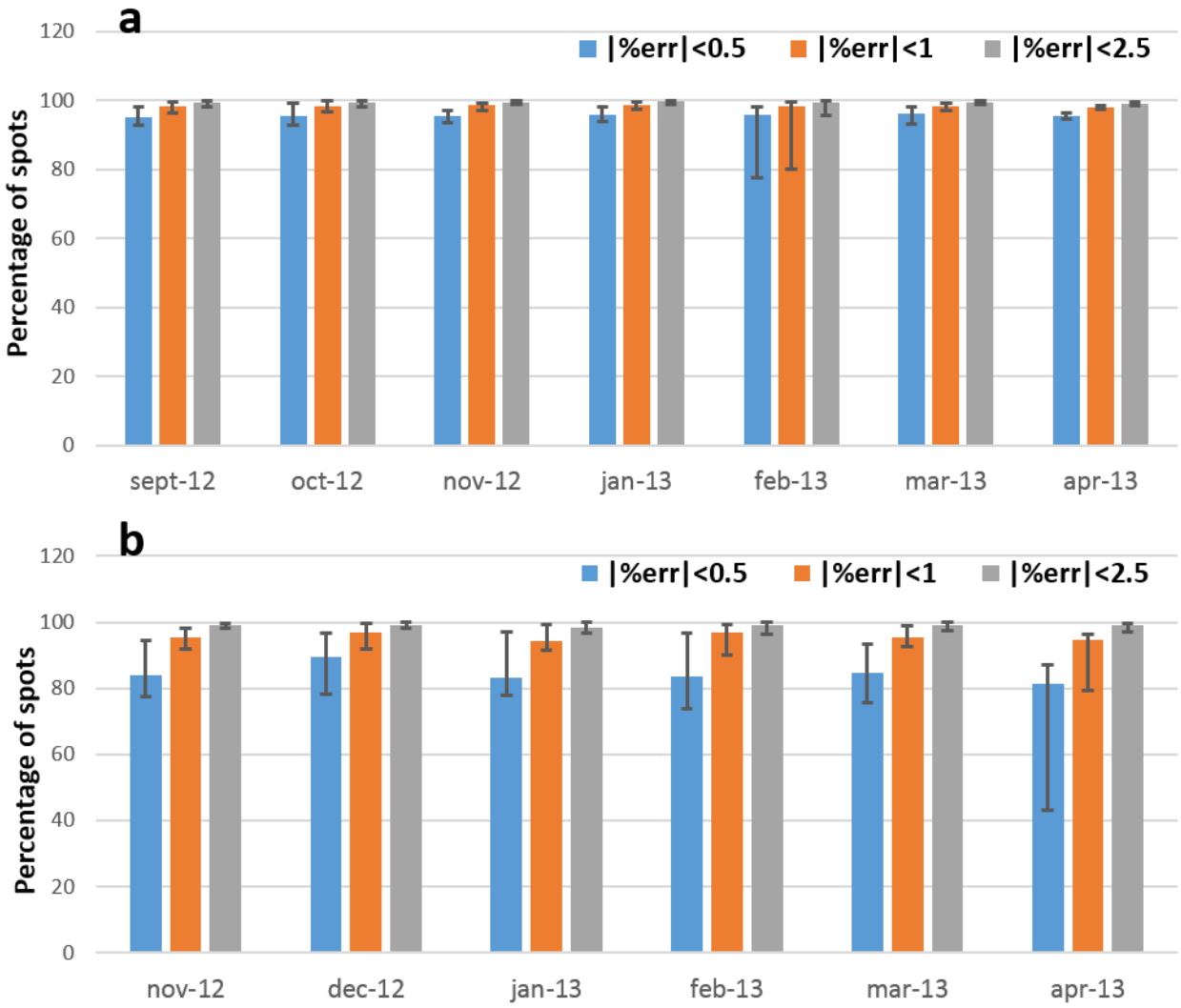


Figure 5. Mean value of the percentage of spots with relative difference between prescribed and delivered number of particles within three different tolerances: 0.5% (blue bars), 1% (orange bars), and 2.5% (gray bars) for all fields treated with protons (a) and carbon ions (b) in room 3. The minimum and maximum percentage values of the fields irradiated in each considered month are displayed as solid vertical bars for the three different thresholds.

Significant daily fluctuations are not observed in the deviations in number of particles: 98% of spots falls within the 2.5% difference, while 94-96% of spots falls within 1.0% difference.

The highest precision threshold of 0.5% results in larger fluctuations: 85-95% of spots in room 1, 91-97% in room 3 for treatments with protons and 75-96% for treatments with carbon ions.

The deviations in the number of particles are dominated by the error on the quantization in the conversion from monitor counts to particles, as one charge quantum corresponds to about 10^4 protons and to about 500 carbon ions. The relative effect of the quantization depends on the number of particles prescribed in the spot. Since the transversal scanning step used in the CNAO clinical practice is 2 mm for carbon ions and 3 mm for protons, the dose (i.e. the number of particles) per spot is on average lower for carbon ions, in respect to protons. Moreover, the increased relative biological effectiveness of carbon ions further reduces the dose required (i.e. the number of particles) per spot for carbon treatments, with respect to proton treatments[16]. As a result, an increased relative error due to the quantization explains the larger fluctuations in the deviations of the number of particles for carbon treatments. Moreover, Fig. 6 shows that the larger relative fluctuations are measured, as expected, for spots with smaller number of particles, and thus reduced clinical relevance.

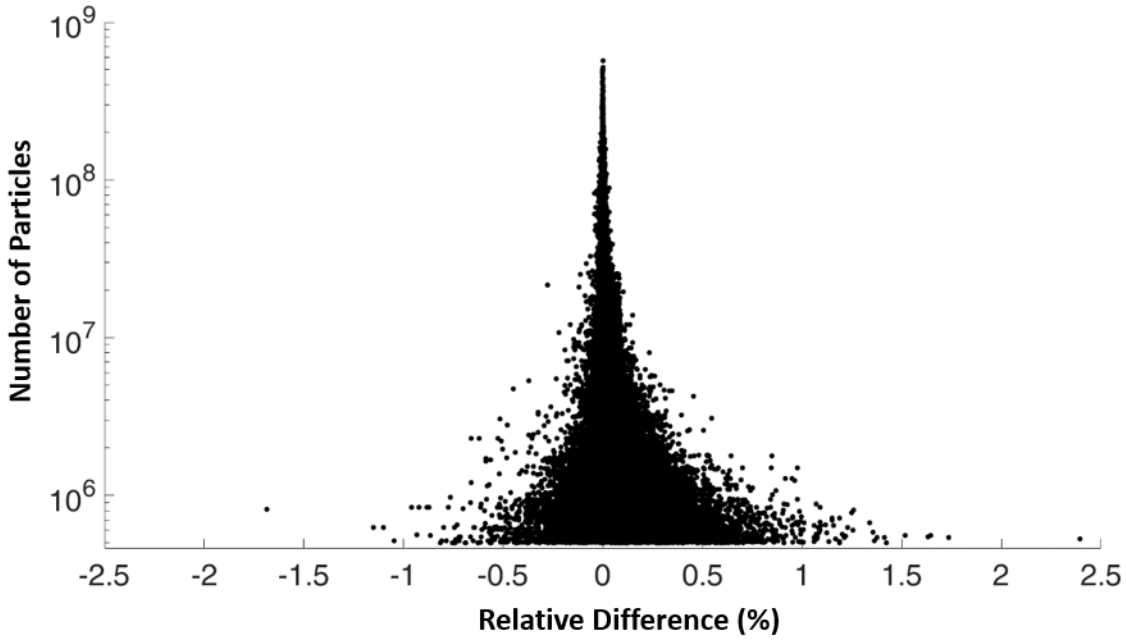


Figure 6. Distribution of the prescribed particles for each spot as a function of the percentage relative difference between prescribed and delivered number of particles (Δparticles/particles) for room 1 (protons).

Impact on delivered dose distributions

Neither the deviations in beam positions nor the ones in number of particles provide any direct information regarding their impact on the delivered dose to the patient, which represents the relevant quantity to evaluate the quality of the treatment. Therefore, both the planned and the measured number of particles and spot positions have been used as input of a dose reconstruction engine of a TPS software[12] to calculate and compare the delivered and the planned physical dose distributions in patient anatomy.

The prescribed dose maps and the delivered ones were compared for several patients, showing on average negligible discrepancies (*passing volume* percentage larger than 99.8% for the sum of all fields) for both protons and carbon ions treatments. It should be emphasized that such an analysis relies on the number of particles and positions at the strip chambers' reference system. Thus, possible deviations at the isocenter could be possible, although within the clinically accepted tolerances, as verified by the daily QA checks described at the end of the previous section *position feedback correction*.

For the sake of concision and clarity, one case study will be reported in the following, chosen because of noteworthy values of gamma index and passing volume percentage for some fractions.

This patient was diagnosed with chordoma of the skull base, with infiltration of the cavernous sinus, treated in room1 between October and December 2012 (protons). Daily dose of 2 Gy (RBE) was given to the tumor target for a total dose of 74 Gy (RBE) in 37 fractions (27 fractions *1st Phase* and remaining 10 as *Boost*). Both *1st Phase* and *Boost* fractions are composed by three fields. The gamma matrix was calculated for all fields.

For this case, both the *1st Phase* and *Boost* fields were re-delivered several times in 2018 on a PMMA block to collect statistic data and evaluate the improvement in delivery uncertainties with respect to 2012, which can be mainly ascribed to the implementation of the position correction feedback loop.

Fig. 7 shows the maximum value of gamma-index among all the voxels and the *passing volume* percentage, i.e. the fraction of voxels with gamma value lower than 1, for each field and for the sum of the three *1st Phase* fields, both for delivered treatment in 2012 (Fig. 7a) and in 2018 (Fig. 7b). Figure 8 shows the same quantities for the *Boost* fields.

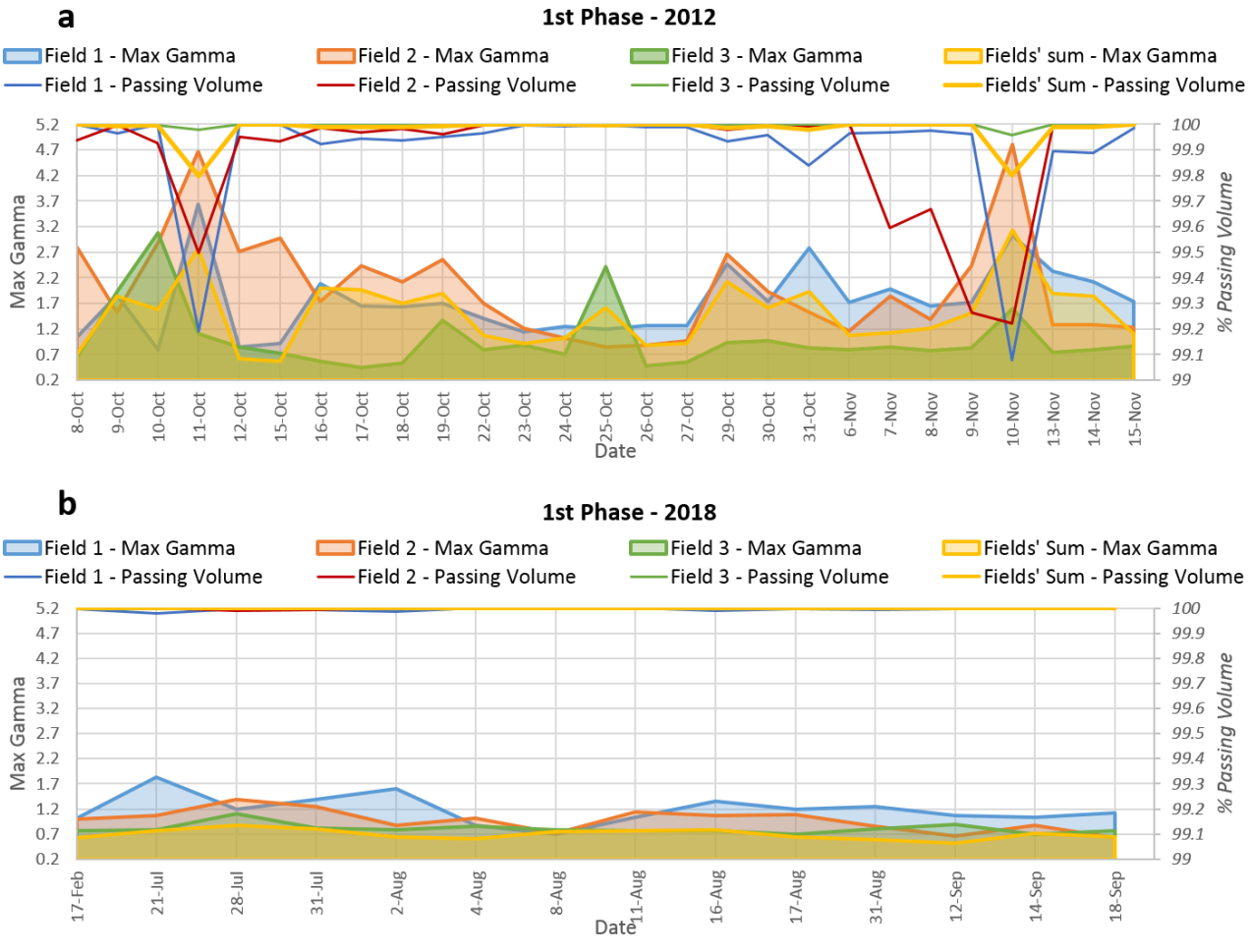


Figure 7: 1st Phase max gamma (area graphs) and percentage of voxels with gamma value lower than 1 (line graphs) for the treatment of one example patient (protons) delivered in 2012 (a) and re-irradiation in 2018 (b).

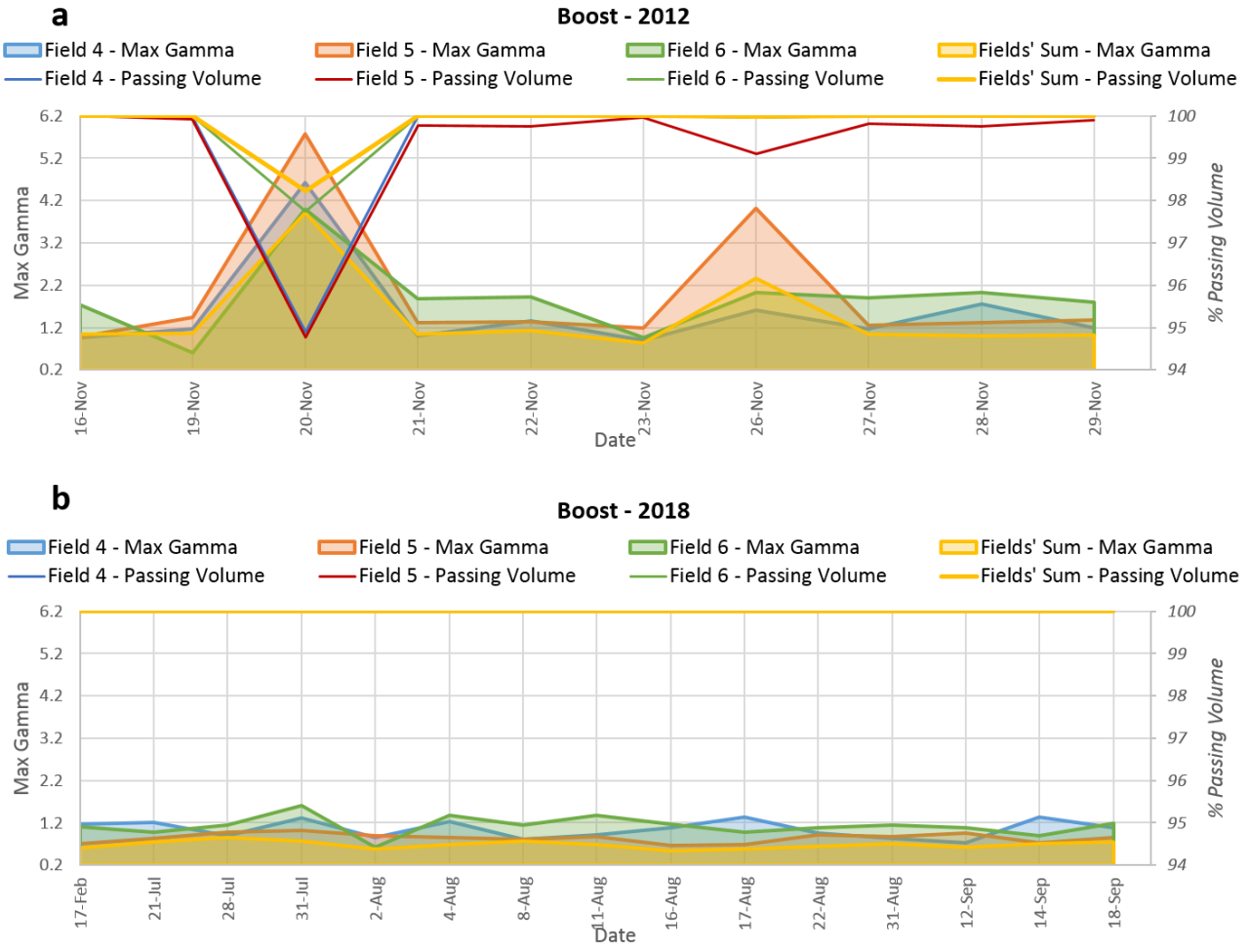
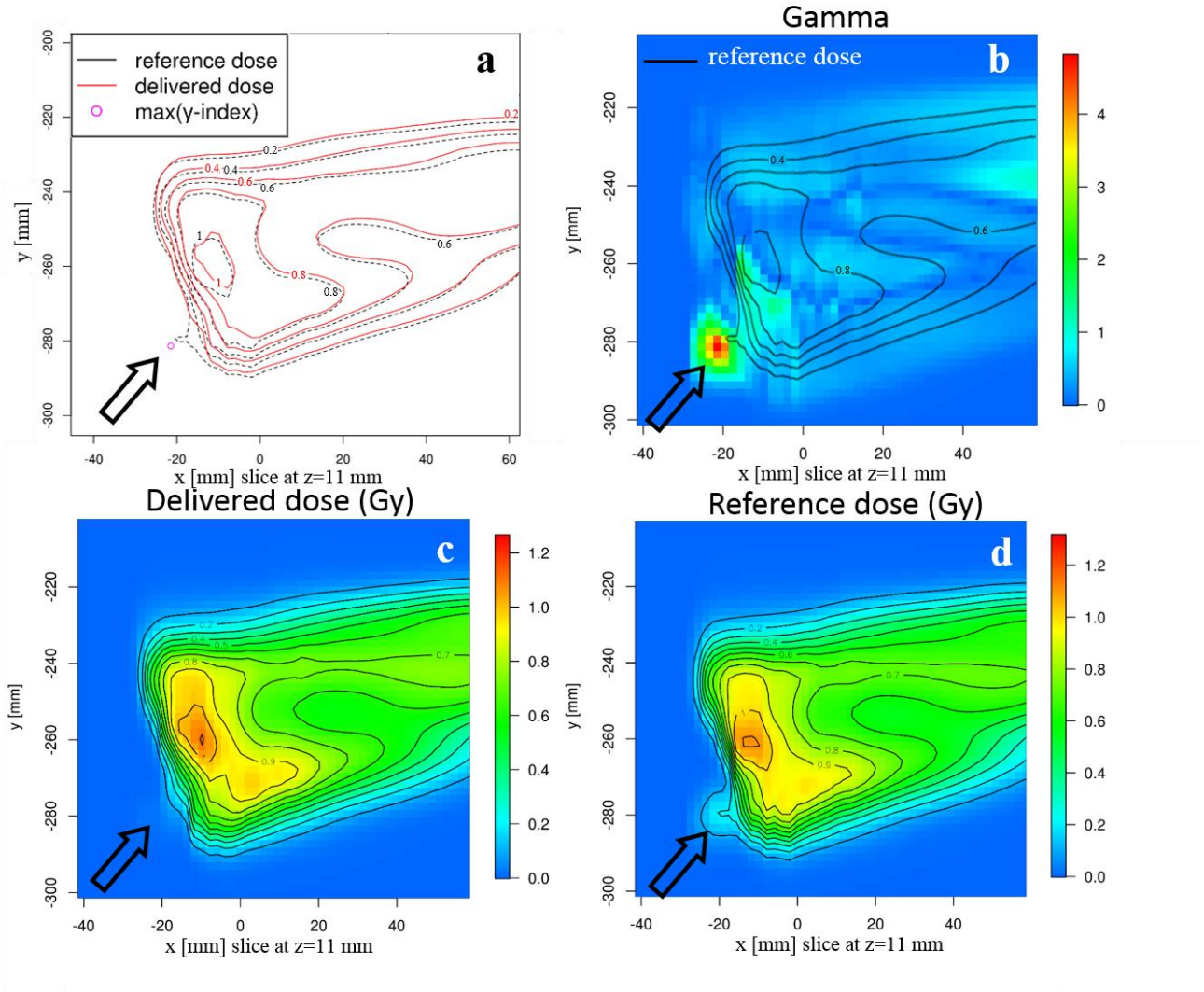


Figure 8. Boost max gamma (area graphs) and percentage of voxels with gamma value lower than 1 (line graphs) for the treatment of one example patient (protons) delivered in 2012 (a) and in 2018 (b).

Maximum values of gamma-index for *1st Phase* fractions irradiated in 2012 are almost always larger than one both for each field (up to a value of 4.8 on November 10 for Field 2) and for the sum of all fields (up to a value of 3.1 on November 10). However, the passing volume percentage is 99.1% in the worst case (Field 1 on November 10) and, what is more important from a clinical point of view, it is always larger than 99.8% for the sum of all fields. This suggests that dose discrepancies are localized in a limited number of voxels. Indeed, the thorough analysis of the 3D distribution of gamma shows that those large values are connected to isolated voxels in regions of low dose and/or high dose gradients, as shown by the isocurves plot in Fig. 9. The clinical relevance of these discrepancies would require the analysis of the volumes at risks, which is out of the scope of the present work.



402

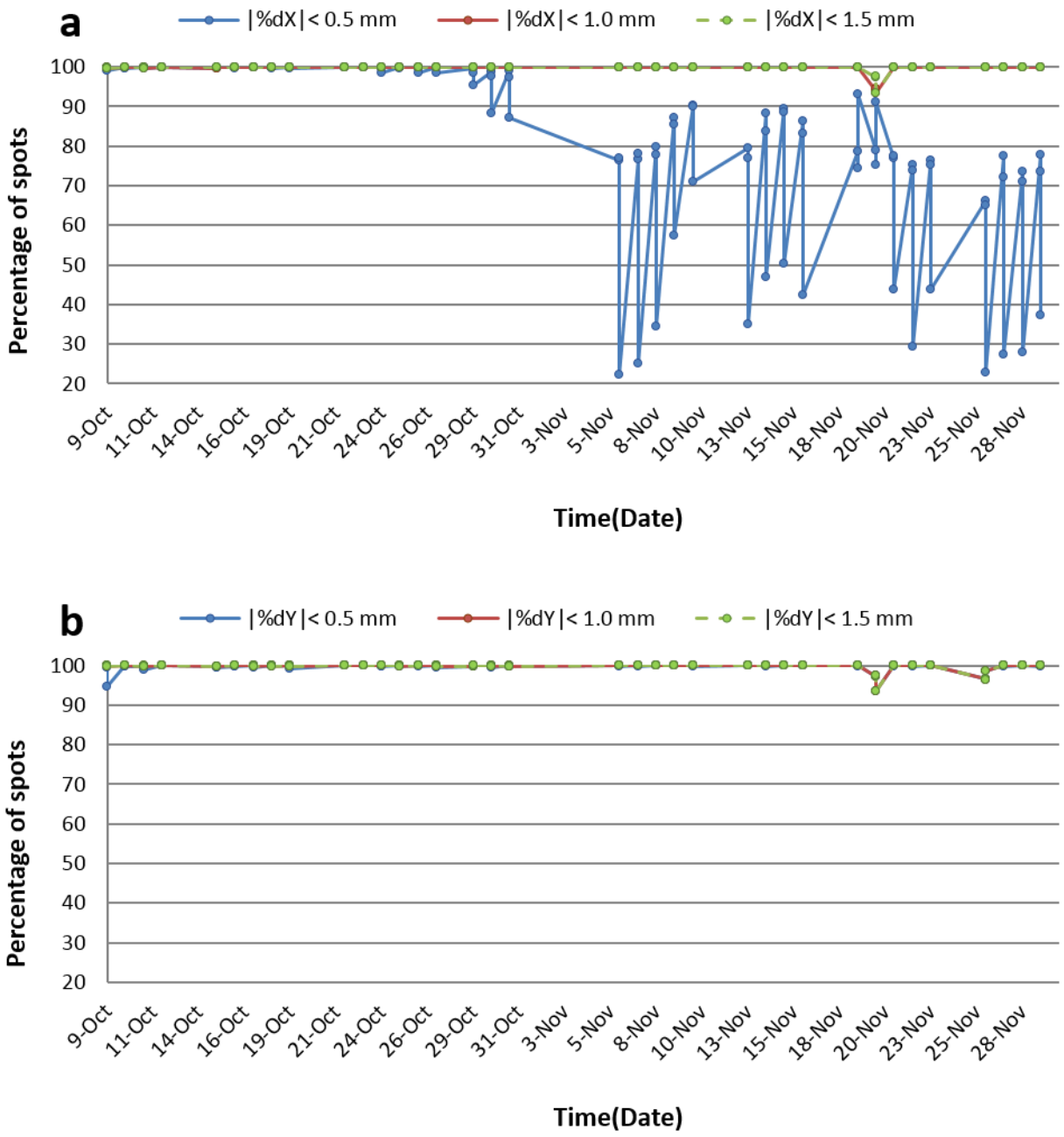
403 ***Figure 9. Isodose curves (a), gamma-index distribution (b), delivered dose (c) and reference dose (d) for the***
404 ***plane x-y at a specific z (z=11 mm) in the CT reference system, for one field. The black arrows points at the***
405 ***pixel corresponding to the maximum gamma value.***

406 On the contrary, the same *1st Phase* fields re-irradiated in 2018 (Fig. 7b) show a maximum value of
407 gamma-index always lower than 1 for the sum of the three fields, reaching 1.8 as worst value for
408 Field 1 on July 21. As before, gamma values larger than 1 are referable to a few single voxels, given
409 the passing rate constantly above 99.99%.

410 Comparing Fig. 7a and 7b, the feedback correction on spot positions seems to improve the day-by-
411 day stability of the delivered dose, leading to an overall better correspondence. However, the
412 improvements are affecting only a limited fraction (~0.2%) of the voxels of the irradiated region

where high dose gradients occur. Considering the magnitude of the dose uncertainties related to patient positioning, changes in patient morphology and moving organs, the improvement in spot position accuracy does not seem to be clinically relevant.

Similar conclusions can be drawn by comparing the *Boost* fractions in Fig. 8. Maximum values of gamma-index for the sum of *Boost* fractions irradiated in 2012 are equal or smaller than 1 for each day of delivery, with the exception of November 20, where the maximum gamma values are 3.9. For all treatment days, the passing rate is almost 100% for the sum of the *Boost* fields, while that percentage drops to 98.2% on November 20. The reason for it is related to an instability, occurring on November 20, of an element of the accelerating system, which led to the observed systematic deviation. Indeed, the graphs of spot position deviations as a function of Boost treatment days (Fig. 10) are in agreement with the high variability observed for the < 0.5 mm threshold in X and Y in the considered period (January 2012 – April 2013), while a reduction of 6% is shown for the fraction of spots within 1.0 and, especially, 1.5 mm tolerance at that date.



426

427 ***Figure 10. Fraction of spots whose position in X (a) and in Y (b) differs from the prescription by less than***
428 ***0.5 mm (blue markers), 1 mm (red markers), 1.5 mm (green markers), for the three Boost fields of the case***
429 ***study under consideration.***

430 **Discussions**

431 The first aim of the present work was to fill up the lack of a detailed retrospective analysis of the DDS
432 performances in the initial period of CNAO clinical activity.

As expected by the very nature of the DDS, which reproducibly works independently of the accelerator, the number of particles was found to be stable. Indeed, the deviations in the number of particles originate from the quantization error in the conversion from monitor counts to particles.

On the contrary, the analysis showed systematic deviations of spot positions within 0.5 mm for only part of the fractions delivered. However, with the exception of the first two months of operation of room 1, deviations were always within 1.5 mm and almost always within 1 mm.

The observed deviations in specific periods were caused by beam lateral offsets and were accurately monitored by the QA measurements daily performed at the isocenter. In order to compensate for this effect and to achieve a precise delivery of the dose to the patient, a constant position offset was added to the initial data conversion from the beam position at the isocentric plane to the currents for the scanning magnet power supplies, to ensure that deviations of the spot positions at the isocentric plane were always within ± 1 mm. These constants were obtained by averaging the corrections over all the beam energy range and were updated daily based on the result of the QA checks performed overnight[7]. If deviations larger than 1 mm for individual energy values were still observed after correction, a complete beam steering correction intervention was immediately requested by medical physicists to accelerator physicists. Excluding cases where deviations larger than 1.5-2 mm were found, the updated steering setting was determined as soon as daily clinical activity was terminated and applied the next day.

To reduce the time for an irradiation and correct for beam position deviations without stopping the irradiation, charged particle facilities have adopted different methods, such as dead reckoning via the algorithmic tables or formulas, beam tuning on the first energy layer, adaptive beam tuning with application of the position offset corrected in the first energy layer to all subsequent layers, and adaptive scanning magnet correction with beam position correction within a scan[17]. The latter has been chosen by CNAO as feedback loop approach, and it is also used by other facilities, such as GSI[18–20], HIT and HIMAC[21].

To complete the investigation of the lateral deviation of the pencil beam during scanning, this work also considers the improvements made by the introduction of the feedback algorithm for the correction of small position deviations, in terms of impact on dose distributions. The implementation of the latter algorithm in the DDS allowed reducing the occurrence of beam interlocks during the treatment, improving the day-by-day DDS stability.

The aim of this study is to verify the efficiency of the beam scanning system in reproducing the expected spot position and number of particles at the location of the monitoring chambers and to quantify the improvement that has been achieved by the introduction of feedback correction, evaluated in terms of gamma-index. It is worth noticing that evaluating the global performance of the DDS would require an independent measurement of spot position and number of particles at the isocenter. This is out of the scope of the present work, and has been reported in the work of Mirandola et al.[7], where the DDS commissioning and the daily QA results and procedures are extensively described.

In order to evaluate the impact of spot position and particle deviations on dose distributions, and the effect of the feedback correction, a representative case was reported. The case consists of a patient treated with protons in 2012, whose treatment was repeated on a PMMA block, in 2018.

A dose calculation tool was fed with the measured number of particles and spot positions from the log files; planned and delivered dose distributions were compared, before and after feedback implementation, through gamma-index calculation.

The variability of the maximum gamma for the real irradiation (2012) was found to be higher than that of the same treatment delivered in 2018. However, the 2012 *passing volume* was found to be larger than 99.8% for the sum of all fields, which is comparable to the 2018's value, with the exception of one day with 98.2% passing volume, probably related to an instability of the accelerating system.

It is worth noting that the clinical effect of the variability found in the maximum gamma for the 2012 irradiation is mitigated by averaging along the number of fractions, and the high percentage of *passing volumes* confirmed the accuracy of the delivery. However, it is equally interesting to consider that in principle the introduction of a position feedback and the increased beam control capability acquired after the first years of clinical experience led to an evident improvement both in the DDS stability, evaluated in terms of gamma index as measure of the impact on dose distributions, and in the stability of operation by reducing the number of interlocks.

Conclusions

The retrospective analysis of the DDS accuracy during the initial clinical activity at CNAO was described, its impact on dose maps was studied, and the effect of the implementation of a position feedback algorithm on the dose distribution was evaluated. No deviation worthy of interest was found between the number of particles prescribed by the TPS and measured by the DDS, while the deviations found in the spot positions should be mainly ascribed to daily fluctuations and accelerator tuning. The introduction of the position feedback, together with the increased beam control capability acquired after the first year of clinical experience, was evaluated in terms of gamma-index of 3D dose maps (prescribed versus delivered) before and after feedback implementation. Although the effect of deviations, and therefore the improvement due to the feedback algorithm, was found to be of moderate clinical impact in terms of dose delivery accuracy, it is worth acknowledging that the introduction of the position feedback increased the stability of operation and minimized the treatment duration by reducing the occurring interlocks.

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Disclosure of Conflicts of Interest

The authors have no relevant conflicts of interest to disclose

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